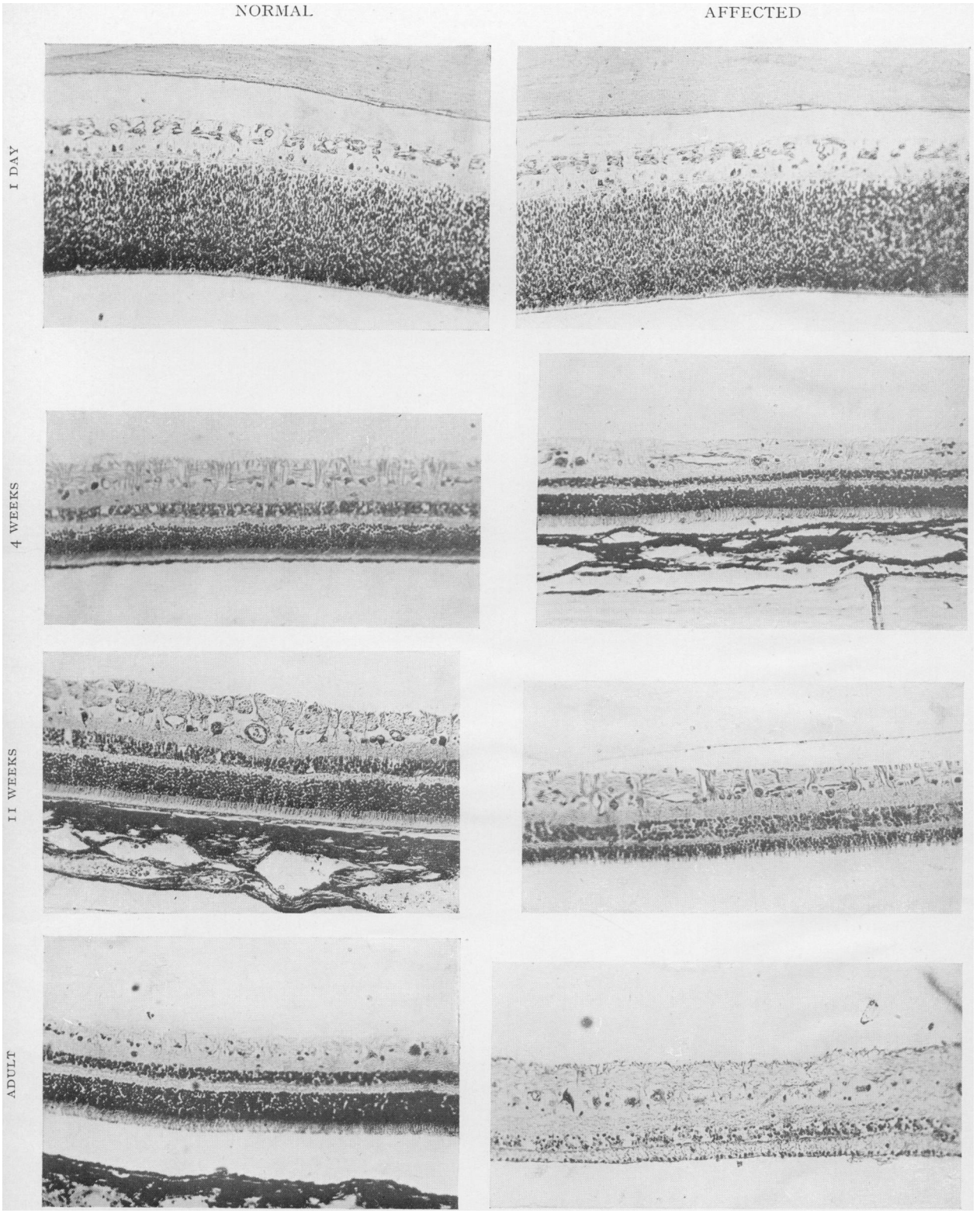

FIG. 1.—Retinal dystrophy in Irish setters. A comparative series of histological sections at different ages in normal and affected animals. Normal sections are shown in the left-hand column, and sections from abnormal animals of the same age in the right-hand column. In the affected animals pathological changes began to appear only after a normal and full post-natal development. (Personal observation.)

PROSPECTS IN THE CONTROL OF GENETIC DISEASE

By ARNOLD SORSBY

TWO fallacies have determined the prevailing attitude to genetically determined disease. It is widely believed that genetically determined affections arise fully developed in the afflicted patient. It is also assumed that such affections are uninfluenced by any other factors. Both these dogmas lead logically to the view that genetic anomalies are beyond treatment, and that the most that can be done is to attempt to eliminate them by eugenic measures.

There is no validity for either belief. Genetic anomalies do not arise fully formed; they have an evolutionary course of their own, comparable to the evolutionary course of a disease of environmental origin—or for that matter to every other process in nature. The evolutionary course of a genetic anomaly is most clearly seen in those genetic affections that arise in post-natal life—the abiotrophies, a classical example of which is retinitis pigmentosa. Here the retina is normal at birth and continues to remain normal for an unknown period—possibly many years. This is borne out by clinical observations on children in families with retinitis pigmentosa. Such children are normal, but some of them subsequently develop the affection. Definite experimental evidence is obtained from a study of the affection as seen in animals. Pure lines of Irish setters can be bred to show the onset of an affection similar to retinitis pigmentosa some weeks after normal development. At birth the retina of the Irish setter is not yet fully differentiated, and it takes about a month before the retina assumes the normal adult appearance. In both normal and affected stock this process occurs in an identical manner. Only after the retina has become fully differentiated in both these types of setters do degenerative changes develop in the animals from the pure line carrying the affection. This is illustrated in Fig. 1. Similar observations are available for the rat and the mouse.

Even the genetic anomaly present at birth shows fundamentally the same process. The only difference is that normal development is interrupted at some period in intrauterine life. This is illustrated by the condition of anophthalmos (lack of eyes) observed in the mouse. Here normal development persists up to the ninth day of pregnancy—halfway through the normal gestation period of the mouse. The severe defect is thus the consequence of a failure in development in a tissue that had been developing normally up to a particular point. Furthermore, a genetically determined congenital anomaly has not necessarily run its full course by birth. Figs. 2a and 2b illustrate the lethal consequences observed in post-natal life from a genetically determined anomaly of cartilage present at birth.

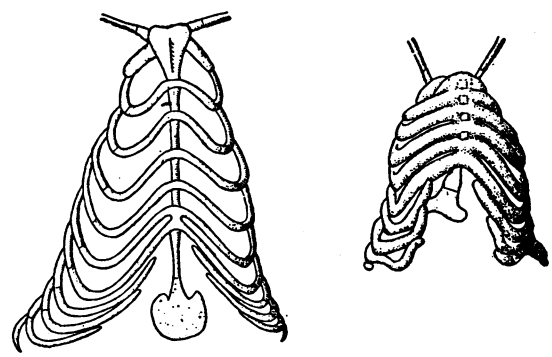

FIG. 2A.—Thoracic basket of a normal rat and a lethal, 22 days old (litter mates).

The second dogma, which holds that genetically determined processes are in fact beyond other influences, is equally ill-founded. The whole of modern genetics emphasizes the facts that no gene has just one effect, and that no gene acts in complete isolation from the influences of other genes. The total genetic constitution of an individual plays its part in the manifestation of the effect of any particular gene; and such

concepts as irregular dominance, expression and penetrance are all indicative of the influences exerted on the manifestation of a particular gene. These influences are not exclusively genetic, such as those due to modifying genes, but are frequently environmental in origin. There is much experimental evidence to illustrate both these processes. Experimentally one and the same gene in a different total genetic environment may be made to behave dominantly or in a

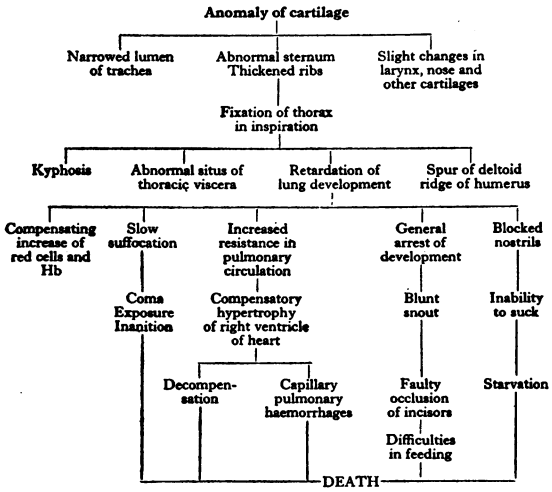

FIG. 2B

[Figs. 2a and 2b are reproduced by courtesy of the author and publishers from "Animal Genetics and Medicine," by Hans Grüneberg. London, 1947. Cassell & Co. By courtesy also of The Royal Society in respect of Fig. 2a.]

recessive manner, environmental influences being kept constant. Likewise environmental factors may also be brought to bear to modify experimentally manifestations of some genes: such classical examples as the development of newly formed black hair in the white Himalayan rabbit kept in the cold, or the development of white fat in rabbits with yellow fat fed on diets lacking particular green stuffs, are instances of many more. In processes approaching pathological states, the suppression in the young rat (genetically disposed to it) of the skeletal anomaly known as bent nose by feeding the mother during pregnancy on a diet rich in vitamin D, is indicative of what may be expected from the rational application of environmental influences once the necessary knowledge is available.

Some Clinical Evidence

Clinical medicine is rich in examples which deny the prevalent fatalism that genetic disease is fixed and immutable. Some of the more significant are enumerated:

(1) *Spontaneous suppression of the manifestations of a pathogenic gene.*—This is clearly seen in the group of affections which show "irregular dominance" or "skipping a generation." The fact that an apparently normal individual in an affected family may yet transmit the affection shows that such an individual must carry the pathogenic gene, though it is not manifested. In fact the gene may be manifest, but such manifestations do not take any clearly pathological form so that the individual is regarded as normal. This is seen in acholuric jaundice: the normal individual is not quite "normal" as is shown by special tests which reveal that his blood corpuscles are abnormally fragile. It is only when the fragility reaches a certain level that the individual becomes handicapped, and is recognized as suffering from a pathological state. Here there is spontaneous suppression sufficiently marked to take the individual out of the pathological range. But full suppression can also occur. This is seen in such a lethal affection as glioma of the retina. "Irregular dominance" also occurs, but the retina of the individual who is himself normal and yet passes on the affection shows no demonstrable differences from the normal.

(2) *The inconstancy of pathological features.*—A further step in suppression, but one not carried to the extent that pathological manifestations are absent, is seen in the inconstancy of manifestation of a pathogenic gene. In the Laurence-Biedl syndrome there is the bizarre combination of mental deficiency, obesity, hypogenitalism, polydactyly and retinitis pigmentosa, but only exceptionally does one and the same individual show all the components of the syndrome. Partial manifestations are the commoner, and the whole syndrome can generally be reconstituted only by a study of several

affected sibs. In each of these suppression has been partial, and sometimes suppression is so marked that the affected individual shows only minimal disturbances.

(3) *Pathological features brought out by environmental factors.*—Such affections as hyperthyroidism appear to be genetically determined, but whether a genetically predisposed individual actually develops the affection is frequently determined by such environmental factors as stress. It is likely that this also applies to such affections as high blood pressure, acute glaucoma, and many others—not excluding such apparently exclusively environmental diseases as the infections. There is much evidence that predisposition to tuberculosis is genetically determined — and whether an individual develops tuberculosis will depend on his mode of living.

(4) *Control of some of the pathological manifestations by environmental agencies.*—Diabetes is a widespread affection, generally recessively inherited. Whilst insulin does not restore the affected individual to normalcy, it does, however, control some of the more deleterious disturbances seen in the affection. It is not beyond all possibility that a fuller understanding of the nature of the affection may give us an agent even more satisfactory than insulin in controlling the pathogenic manifestations. An approach to something like a radical cure in a genetic affection is seen in the effects of splenectomy in acholuric jaundice. Here, removal of the spleen acts as a controlling mechanism on the manifestation of the disease.

(5) *The prevention of genetic disease.*—The recognition of Rh. blood groups, and the dire consequences to the newborn child of incompatible blood groups in the parents, is the latest of means available on the basis of adequate knowledge to prevent by simple measures ravages that would otherwise be unavoidable.

The Future

Enough is already known to make an anachronism of the current fatalism towards genetically determined disease. Further progress depends on detailed knowledge. As a portent of future developments, the studies on phenylalanine metabolism are suggestive. Normally this relatively simple amino-acid becomes converted by a series of steps into water and carbon dioxide. This is shown in Fig. 3, from which it is seen that such a severe anomaly as mental deficiency associated with phenylketonuria develops if the

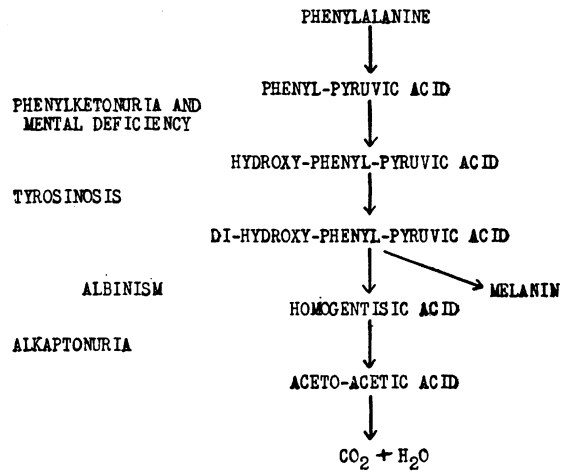

FIG. 3

conversion process fails at an early stage. Albinism is seen if the failure occurs at a later stage, and alkaptonuria at a still later stage. To what extent similar disturbances occur in other genetic anomalies remains to be established. What is significant of such studies is that they open the possibility of modifying these relatively simple chemical disturbances at a stage before pathological ravages have set in.